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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/899,303	07/06/2001	Geert Maertens	2752-52	3515

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EXAMINER	
LI, BAO Q	

ART UNIT	PAPER NUMBER
1648	24

DATE MAILED: 01/14/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/899,303	MAERTENS ET AL.	
	Examiner	Art Unit	
	Bao Qun Li	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 November 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *68-70,73,74,76,77,79,85-91 and 95-101* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *68-70,73,74,76,77,79,85-91 and 95-101* is/are rejected.

7)☒ Claim(s) *73, 76* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *16&20*.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Claims 68-70, 73-74, 76-77, 79, 85-91 and 95-100 are pending.

Response to Amendment

This is a response to the amendment, paper No. 22, filed 09/25/03. Claims 1-67, 71-72, 75, 78, 80-84 and claims 92-94 have been canceled. Claims 68-**70, 73-74, 76**-77, 79, 85, 86-91 and 96 have been amended. New claims 97-101 are added, Claims 68-70, 73-74, 76-77, 79, 85-91 and 95-100 are pending and considered before the examiner.

Please note any ground of rejection(s) that has not been repeated is removed. Text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

Election/Restrictions

The petition filed on August 21, 2003 has been notice and granted in that all pending claims with full scope of all sequences listed in claims 96 and 97 are considered before the examiner.

Information Disclosure Statement

1. Since Applicants prove the proper foreign patent document numbers, the IDS, paper no. 16, filed on March 27, 2003 has been considered and returned to the Applicants with this Office Action.

Claim Objection

2. Claim 73 is objected to because of the following informalities: the claim 67 recited in the claim 73 should be deleted because claim 67 was canceled by the applicant previously.

3. Claim 76 is objected in that the 1st "," should be removed.

4. Appropriate correction is required.

Claim Rejections - 35 USC § 102

3. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

4. Claims 70, 73, 75, 76, 87, and 95-97 are still rejected under 35 U.S.C. 102(e) as being anticipated by Watanabe et al. (US Patent No. 5,610,009A) on the same ground as stated in the previous Office Action.

5. Applicants traverse the rejection and submit that internal deletion of amino acids 260-296 is not equal to or within the range claimed in the present invention and all sequences used by Watanable et al. are derived from HIV-1, type 1a isolate. SEQ ID NO: 7 of the current invention, being derived from a type 1b HCV isolate. Moreover, the vector disclosed by Watanable is an adenovirus vector.

6. Applicants' argument has been considered; however, it is of found persuasive because the claims are not sorely directed to the nucleic acid sequence derived from HCV type 1b or SEQ ID NO: 7, they are broadly directed to any part of the SEQ ID NO: 7. Since HCV type 1a contains certain part, which has 100% homology to the HCV 1a. Moreover, the truncated amino acid residue range from 260-296 includes the claimed range of 264-293 in claim 70. In addition, claim 70 does not limit the vector is a vaccinia vector. Moreover, Watanable et al. also disclosed a clone pHCV 416, which constructed by removing an internal hydrophobic region residing on Acyl-Acyl fragment and only contains the amino acid residues 192 to 256, 297 to 336 and 393 to

654. Therefore, the amino acid residues 264 to 293 in which a hydrophobic region is removed, and an E1 region is included. Therefore, the rejection is maintained.

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. Claims 68-70, 73-74, 76, 79, 87-88, 91 and 95-96 are still rejected under 35 U.S.C. 103(a) as being unpatentable over Lanford et al. (Virology 1993, Vol. 197, pp. 225-235), Ralston et al. (J. Virol. 1993, Vol. 67, pp.6753-6761), Watanabe et al. (US Patent No. 5,610,009A) and Ford et al. (Protein expression and purification 1991, Vol. 2, pp. 95-107) under the same ground as stated in the previous Office Action.

9. Applicants traverse the rejection by arguing that the claimed invention is not taught and suggested by the combination of cited art.

10. Applicants' argument has been considered; however, it is not found persuasive because the combinations of the reference teach each and every imitation of claims.

11. Lanford et al. teach a recombinant live eukaryotic vector, carrying an HCV E1 protein fragment encoding HCV amino acids 117-386, which contains part of SEQ ID NO: 7. 1st hydrophobic domain located at the carboxyl terminal located at 340 aa was truncated. The 5' of inserted HCV cDNA fragment contains an ATG for initiation site and the 3' contains a TAA termination codon. The expressing vector is baculovirus vector, which allows the expression of an HCV E1 as a single envelope viral protein. These teach all limitation of 68, 69, 70, 73, 87, 95, 96, 97.

12. Ralston et al. teach to use a vaccinia viral vector for expressing HCV E1 protein (See entire document), which meet the limitation of 68 and 88.

13. Regarding the addition a histidine codon at the C-terminal of claim 74, it is well know in the art that addition of a tag, such as histidine tag has been used as routine for the purpose of purification of a fusion protein as evidenced by Ford et al. which is a powerful technique based on interactions of some proteins with immobilized transition metal ions. They particularly teach that the technique is involved by adding poly(his) tails ranging in length from 2 to 6 residues and fused to either the N-terminus or C-terminus (See section of 7 Poly(His) Tails on page 100), therefore, it greatly benefit for the purification process by using a metal affinity chromatography (IMAC). Therefore, Ford et al. teach the limitation of claim 74.

14. Regarding to the limitation of claim 70 that HCV E1 protein contains a deletion at the amino acid sequence between the position of 264-293, plus or minus 8 amino acids (272-301 for plus amino acids or 256-285 for minus 8 amino acids), Watanable al. teach a recombinant live eukaryotic adenovirus vector carrying deferent fragments of HCV E1 protein. Some of them start with the amino acid position 192 originated from the whole genome of HCV cDNA and ends with amino acids 337 or 383 (See lines 16-29 on col. 12), in which a carboxyl terminal was truncated at residue 260-296 to remove the internal hydrophobic region, which is within the claimed region between positions 264-293, plus or minus 8 amino acids . Moreover, Watanable et al. also disclosed a clone pHCV 416, which constructed by removing an internal hydrophobic region residing on Acyl-Acyl fragment and only contains the amino acid residues 192 to 256, 297 to 336 and 393 to 654. Therefore, the amino acid residues 264 to 293 in which a hydrophobic region is removed, and an E1 region is included (See example 1 on col. 11 and 12). Therefore, the rejection is maintained.

15. Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention was filled to be motivated by the recited references and to combine the disclosures taught by Lanford et al. Ralston et al. Watanable et al. and Ford et al. to make a recombinant vector for expressing an HCV E1 protein fused with a histadine tails at its C-terminal and further containing a truncation in the hydrophobic domain as taught by Watanable et al. with highly expected result. As there are no unexpected results have been provided, hence the claimed invention as a whole is prima facie obvious absence unexpected results. The rejection is maintained.

16. **New ground Rejection:**

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

17.

1. Claims 77 and 98-100 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. In the instant case, the specification does not teach that claimed products are enable to be used as vaccine.

18. The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the application coupled with information known in the art would undue experimentation (See United States v. Theketronic Inc., 8USPQ2d 1217 (fed Cir. 1988). Whether undue experimentation is required is not based upon a single factor but rather a conclusion reached by weighting many factors. Theses factors were outlined in Ex parte Forman, 230 USPQ 546 (Bd. Pat. App. & Inter. 1986) and again in re Wands, 8USPQ2d 1400 (Fed. Cir. 1988). These factors include the following:

19. 1) & 2) State of art & Unpredictability of the filed.

20. HCV vaccine has been studied with all individual HCV encoded proteins or combination thereof. However, none of them is approved as a HCV vaccine so far as evidenced by Liang et al. (Annual of internal Medicine 2000, Vol. 132, No. 4, pp. 296-305). They indicate that development of HCV vaccine is extremely unpredictable because the following problems: (1) HCV virus is characterized with quasi-species due to a high rate of mutation in the hypervariable region of the envelope proteins; (2) the hypervariable region of envelope proteins contains a principal neutralization epitope responsible for inducing the neutralizing antibody; (3) the neutralizing antibody of HCV E1 or E2 develops slowly and achieves only modest titers during primary infection and tends to be a short-lived antibodies. Consequently, it emerges too late to

prevent HCV infection; (4) the immunologic responses that correlate with the HCV protection and disease progression have not been clearly defined. Even with accepted animal model chimpanzees, it has been demonstrated that challenge vaccinated chimpanzees with a homologous or heterologous strain of HCV resulted in re-infection, suggesting an absence of protective immunity after natural infection; (5) Studies have shown that a vigorous multispecific cellular immune response involves in the HCV infection and an ideal HCV vaccine should not only elicit high-titer, long-lasting, and broadly directed anti-envelope antibodies but also a vigorous, multispecific cellular immune response. In particular, conserved T-cell epitopes in the core, NS3, and NS4 regions should be targeted. In contrast, the claimed invention only directed to use vector expressing an E1 protein or fragment of E1 protein as vaccine composition.

21. 3) &4). Number of working examples and Amount of guidance.

22. The specification only teaches how to express recombinant E1 protein fragment and expression of the mutated E1 protein by using a recombinant vector. There is no any in vivo working example teaching that any claimed vector that expresses an E1 protein or any fragment thereof as listed in claims is able to produce a protective immune response against HCV infection in an art accepted animal model.

23. 5) Scope of the claims.

24. The claims broadly read a HCV vaccine for preventing HCV infection.

25. 6) & 7) Nature of the invention and Level of skill in the art:

26. The invention involves one of the most complex and unpredictable fields of developing HCV vaccine. The requirement of the level of the skill in the art is very high. As noted by some of the preeminent researchers on HCV, a significant hurdles remain to be overcame in order for the skilled artisan to practice successful the full scope of the claimed invention.

27. Given the above analysis of the factors, which the courts have determined, are critical in asserting whether a claimed invention is enabled, it must be considered that the skilled artisan would have had to conduct undue and excessive experimentation in order to practice the claimed invention.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

28. Claims 95-98 and 100 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

29. Claims 95, 96, and 97 are vague and indefinite in that the metes and bounds of "parts thereof " are not defined. Claims are interpreted in light of the specification; however the specification does not define what is the definition of "parts of thereof" are.

30. M.P.E.P. 2172 recites that Although an essential purpose of the examination process is to determine whether or not the claims define an invention that is both novel and nonobvious over the prior art, another essential purpose of patent examination is to determine whether or not the claims are precise, clear, correct, and unambiguous. The uncertainties of claim scope should be removed, as much as possible, during the examination process. The inquiry during examination is patentability of the invention as applicant regards it. If the claims do not particularly point out and distinctly claim that which applicants regard as their invention, the appropriate action by the examiner is to reject the claims under 35 U.S.C. 112, second paragraph. In re Zletz, 893 F.2d 319, 13 USPQ2d 1320 (Fed. Cir. 1989). M.P.E.P. further recites: If the language of the claim is such that a person of ordinary skill in the art could not interpret the metes and bounds of the claim so as to understand how to avoid infringement, a rejection of the claim under 35 U.S.C. 112, second paragraph would be appropriate. See Morton Int 'l, Inc. v. Cardinal Chem. Co., 5 F.3d 1464, 1470, 28 USPQ2d 1190, 1195 (Fed. Cir. 1993)..

31. In the instant case, the claimes sequences encoding more than 600 base pairs of nucleic acid, a person skill in the art cannot define what the metes and bounds of claimed product. Applicants are suggested to amend claim with a defined structural of the claimed product to overcome the rejection. This affects the dependent claims 98 and 100.

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No prior art teach or suggest using an avipox or Ankara Modified virus as a vector to express the particular fragment of HCV E1 or full length HCV E1 or truncated HCV E glycoprotein. However, they are not in the condition for allowance because they depend on rejected claims.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bao Qun Li whose telephone number is 703-305-1695. The examiner can normally be reached on 7:00 to 4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel can be reached on 703-308-4027. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4242 for regular communications and 703-308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Bao Qun Li
Art Unit 1648.
January 08, 2004.

James C Housel 1/12/04

JAMES HOUSEL
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